REMARKS

Claims 1-16, 21-29, 31-34, and 37 are pending in the application. No amendments have been made by the present response and no new matter has been added.

35 U.S.C. §103(a) (Obviousness)

At pages 2-3 of the Advisory Action, claims 1-4, 6-16, 29, 32-34, and 37 were finally rejected as allegedly unpatentable over Papahadjopoulos et al, U.S. Patent No. 6,803,053 ("Papahadjopoulos") taken with Rolland et al., U.S. Patent No. 6,040,295 ("Rolland") and further in view of Lunsford et al., U.S. Published Application No. 2002/0182258 ("Lunsford"). In addition, claims 1-4, 6-16, 26, 29, 32-34, and 37 were finally rejected as allegedly unpatentable over Papahadjopoulos taken with Rolland and further in view of Mathiowitz et al., U.S. Patent No. 6,677,313 ("Mathiowitz"). The present Advisory Action stated that the rejections have been maintained, at least in part, for reasons of set forth in the final Office Action dated January 24, 2008 (which relied in part on the rejections made of record in the prior Office Actions dated October 6, 2005, and February 22, 2007).

The Office Action dated October 6, 2005, stated that "it would have been obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos *et al.*" The Office Action dated October 6, 2005, also used substantially similar language in the obviousness rejection citing the combination of Papahadjopoulos, Rolland, and Mathiowitz.

In the response to the final Office Action, applicants addressed in detail the rejection based on the remarks above as well as the additional assertion in the final Office Action that "there is no reason not to include or substitute a hydrophilic polymer (e.g., PEG-DSPE) in the microparticle compositions."

The present Advisory Action does not appear to maintain the original basis for rejection quoted above. Instead, the Advisory Action states that

> [a] person of ordinary skill in the art would not need to incorporate the components of the microparticle of Papahadjopoulos et al., into those of Lunsford or Mathiowitz. Rather the references of Lunsford and Mathiowitz were used to supply the deficiencies in Papahadjopoulos et al. relating to microparticle diameter and antigenic peptide for delivery to mucosal tissue.

The comments reproduced above from the Advisory Action appear to be at odds with the basis for rejection in the previous Office Actions, i.e., that "it would have been obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos *et al.*" (emphasis added). It is applicants' understanding that the Examiner no longer maintains this previous basis for rejection and has substituted it with the new assertion reproduced above. The following comments are directed to this new basis for rejection.

Independent claim 1 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule, wherein the microparticle is not encapsulated in a liposome and the microparticle does not comprise a cell. Independent claim 21 is directed to a microparticle that is less than about 100 microns in diameter and contains: (i) a polymeric matrix; (ii) a lipid having a pKa of less than about 2.5; and (iii) a nucleic acid molecule.

As noted above, the Advisory Action states that "the references of Lunsford and Mathiowitz were used to supply the deficiencies of Papahadjopoulos et al. relating to microparticle diameter and antigenic peptide for delivery to mucosal tissue." The Advisory Action contains no assertion as to any reason why a person of ordinary skill in the art would have modified a composition of Papahadjopoulos to include features of the compositions of Lunsford and Mathiowitz relating to microparticle diameter and antigenic peptide for delivery to mucosal tissue. Because the Examiner has failed to articulate *any* reason for making this combination, the rejection does not establish a *prima facie* case of obviousness.

Although the Advisory Action lacks any stated reason as to why a skilled artisan would have made the modification now suggested by the Examiner, applicants offer the following comments on the proposed combination in an effort to facilitate resolution of this matter.

Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer (such as polyethylene glycol distearoyl phosphatidylethanolamine; "PEG-DSPE"). As applicants have established in replies to previous office actions, Papahadjopoulos differs from the claimed microparticles in at least the following respects: (1) there is no indication in Papahadjopoulos that a hydrophilic polymer described therein forms a "polymeric matrix" in the reference's cationic lipid:nucleic acid complexes; (2) Papahadjopoulos does not disclose a composition containing a polymeric matrix and a lipid having a pKa of less than about 2.5; and (3) Papahadjopoulos does not disclose a non-liposome composition that is less than about 100 microns in diameter. In contrast to Papahadjopoulos's lipid:nucleic acid complexes, Lunsford and Mathiowitz describe polymeric microparticles. Given the fundamental structural differences between the lipid:nucleic acid complexes of Papahadjopoulos and the polymeric microparticles of Lunsford and Mathiowitz, the skilled person would have had no reason to have made the modifications now suggested by the Examiner. Nothing in Lunsford or Mathiowitz would have led the skilled artisan to modify the lipid:nucleic acid complexes of Papahadjopoulos so as to result in the claimed microparticles.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 1-4, 6-16, 26, 29, 32-34, and 37.

At page 3 of the Advisory Action, claims 21-24, 26-28, and 31 were finally rejected as allegedly unpatentable over Lunsford in view of Papahadjopoulos. The present Advisory Action stated that the rejections have been maintained, at least in part, for reasons of set forth in the final Office Action dated January 24, 2008.

The Office Action dated January 24, 2008, stated that "it would have been *prima facie* obvious for one of ordinary skill in the art to include PEG-DSPE disclosed by Papahadjopoulos *et al.* in the microparticle of Lunsford et al., with a reasonable expectation of success, to produce the microparticle of the instantly claimed invention."

Lunsford describes microparticles containing a polymeric matrix, a nucleic acid, and a cationic lipid or a phospholipid. As acknowledged in the final Office Action, Lunsford does not describe including in a microparticle a lipid (such as PEG-DSPE) having a pKa of less than

about 2.5. For the following reasons, applicants respectfully submit that Papahadjopoulos would not have provided the skilled person any reason to include PEG-DSPE in a microparticle of Lunsford.

Papahadjopoulos describes cationic lipid:nucleic acid complexes containing, among other components: (a) a cationic lipid; (b) a nucleic acid; and (c) a hydrophilic polymer. The exemplary "cationic lipids" listed by Papahadjopoulos (at column 11, lines 6-7) include DODAC, DOTMA, DDAB, DOTAP, DC-Chol, and DMRIE. Nowhere does Papahadjopoulos suggest that PEG-DSPE can or should be used as the cationic lipid component in its complexes. As a result, even if one were to select any one of the "cationic lipids" described by Papahadjopoulos as useable as the cationic lipid component of its cationic lipid:DNA complexes, PEG-DSPE would not have been the result of such a selection. Therefore, even if a person of ordinary skill in the art were to select a "cationic lipid" component disclosed by Papahadjopoulos and use that cationic lipid as the cationic lipid in a microparticle composition of Lunsford, such a modification would not result in the claimed compositions.

Papahadjopoulos describes PEG-DSPE as an example of the "hydrophilic polymer" component of its complexes (i.e., not as an example of the "cationic lipid" component) and states that PEG-DSPE can be included in its complexes as a means to prevent aggregation of the complexes and thereby enhance their shelf life. Because this anti-aggregation function of PEG-DSPE in the cationic lipid:nucleic acid complexes of Papahadjopoulos would have been irrelevant in the polymeric microparticles of Lunsford, the skilled person would have had no reason to make the modification proposed in the Office Action.

In view of the foregoing comments, applicants respectfully submit that the cited references do not render obvious any of claims 21-24, 26-28, and 31.

CONCLUSION

Applicants respectfully request that all claims be allowed in view of the remarks contained herein.

Enclosed is a Petition for Extension of Time. The extension of time fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 08191-018001.

Respectfully submitted,

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